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Predictors of Left Ventricular Performance after Valve Replacement in Children and Adolescents with Chronic Aortic Regurgitation

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Abstract. Aortic valve replacement has been recommended in patients who have severe symptoms, in patients with extreme left ventricle (LV) dilatation (end diastolic dimension >4 SD above normal) or LV ejection fraction <50%. However, the occurrence of advanced symptoms or severe LV dilatation raises concern about irreversible LV dysfunction. This study sought to determine the influence of preoperative symptoms, LV size and function on mortality, and postoperative LV performance in children and adolescence after valve replacement for aortic regurgitation (AR). A total of 49 patients 18 years old or younger (mean, 13.9 ± 3) who underwent valve replacement for chronic AR between 1991 and 2001 were followed up for 1–10 years (mean, 3.3 ± 2.1). Baseline and postoperative characteristics were compared between 13 patients (group 1) with extreme LV dilatation and 34 patients (group 2) with a lesser degree of LV enlargement. Preoperative low ejection fraction ($p < 0.008$), extreme LV dilatation ($p < 0.05$), and LV end systolic dimension >4 SD above normal ($p < 0.05$) were predictors of persistent LV dysfunction. Extreme LV dilatation ($p < 0.0003$), LV end systolic dimension ($p < 0.0007$), and reduced LV ejection fraction ($p < 0.01$) predicted persistent LV dilatation. In the setting of chronic AR, preoperative symptoms, LV systolic function, and LV internal dimensions are the main predictors for persistent LV dysfunction and dilatation. Surgical correction should be performed before LV systolic dysfunction and/or extreme LV enlargement occurs.

Key words: Chronic aortic regurgitation — Aortic valve replacement

Aortic regurgitation (AR) can be corrected successfully with aortic valve replacement (AVR). Because of the relatively high incidence of postoperative left ventricular (LV) dysfunction, objective indexes of LV size and function have been recommended to guide the timing of AVR [1, 5, 7, 11, 13]. Despite some controversy, it is a common belief that surgery for chronic AR should be performed before a considerable decrease in systolic function and severe enlargement of the LV has occurred, even in asymptomatic or mildly symptomatic patients [1, 3, 5, 7, 11, 13]. Additionally, there are a group of patients with chronic severe AR who are symptomatic [New York Heart Association (NYHA) functional class III/IV] and thus need valve replacement irrespective of LV size [8, 13].

Despite several previous studies on the evaluation of the predictive value of clinical and echocardiographic parameters, appropriate timing of surgery is still a controversial and sensitive issue [5, 7, 11, 13]. Because of the physical growth of children, early operation increases the possibility for a later operation, which will be more risky and hazardous. On the other hand, potential benefits of surgical intervention cannot be attained when corrective surgery is performed too late and such patients are at risk of persistent LV dilatation and progressive heart failure. Accordingly, making appropriate decisions regarding surgical timing for children is more difficult than for adults. However, a number of previous reports have evaluated the importance of clinical and hemodynamic parameters in adults, who usually suffer from multiple other pathologic conditions (e.g., coronary artery disease, diabetes mellitus, and hypertension). The American College of Cardiology and the American Heart Association published the guidelines for the management of patients with valvular heart disease [2]. According to this guideline, the indication for surgery in children with isolated AR is similar to that for adults; that is, NYHA functional class III/IV

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symptoms, LV dysfunction (LV ejection fraction $< 50\%$), or progressive LV enlargement (end diastolic dimension > 4 SD above normal for body surface area and weight). To our knowledge, postoperative improvement of symptoms and ventricular function were not completely evaluated. Thus, we evaluated the importance of preoperative clinical, hemodynamic variables for persistent ventricular dysfunction after aortic valve replacement in children and adolescents. In this study, we attempt to determine the appropriate timing of aortic valve replacement irrespective of etiology of aortic regurgitation, before irreversible myocardial damages develop.

Materials and Methods

Patients enrolled in this study all had the following criteria: (1) 18 years of age or younger; (2) chronic severe AR as diagnosed by echocardiography and aortography (grade III/IV regurgitation); (3) surgical replacement of aortic valve in our institution between 1991 and 2001; (4) adequate preoperative echocardiography, with dimension and function measured within 3 months of operation; and (5) postoperative echocardiography, with internal LV diameters and function measured approximately 1 year after surgery. Excluded were those patients with (1) associated significant aortic stenosis (a pressure gradient exceeding 40 mmHg), (2) concomitant moderate mitral or tricuspid valve regurgitation or stenosis; and (3) large ventricular septal defect (VSD) with significant left-to-right shunt ($Q_P/Q_S > 2/1$). Patients who underwent aortic root replacement at the time of AVR were not excluded.

Echocardiographic evaluation was performed a median of 25 days (up to 3 months) before the operation. Because of known gradual postoperative improvement of LV internal diameters and function, the echocardiograms used for analysis of these parameters were obtained approximately 1 year after operation (mean, 405 days). Standard echocardiographic studies were carried out according to the American Society of Echocardiography recommendations [12]. M-mode measurements of LV internal dimensions and ejection fraction (EF) were guided by two-dimensional echocardiography. For each case, normal limits of ventricular diameter (mean value $\pm$ SD) were calculated using the equation introduced previously [6]. The echocardiographic data of patients were compared against nomograms [12]. In our study, similar to previous reports, LV end diastolic dimension > 4 SD above normal was considered as extreme LV dilatation [3, 5, 7, 12]. Then, patients were divided into two groups on the basis of LV end diastolic dimension. Patients with extreme LV dilatation were classified in group 1. Patients with lesser degrees of LV enlargement were considered as group 2. Postoperative end diastolic dimension greater than tolerance limit for weight and age was considered as persistent LV dilatation [6, 7, 12]. Postoperative LV dysfunction was defined as the presence of cardiac failure or LVEF $< 50\%$ [3, 5, 11]. NYHA functional class was determined according to symptoms and functional impairment at the time of preoperative evaluation regardless of previous symptoms and history. Follow-up was completed for patients up to 2001 or death. Operative mortality was defined as death occurring within the hospitalization period or within 30 days of operation.

Statistical Analysis

Group statistics were expressed as mean value $\pm$ SD. Between-group comparison of the changes in LV echocardiographic variables from preoperative to postoperative measurements were carried out using one-way analysis of variance for repeated measurements and a group variable. Group comparisons (group 1 vs group 2) were performed with a standard *t*-test, Chi–square test, or Fisher's exact test, when appropriate. The endpoints were operative mortality (death occurring within 30 days after operation), postoperative EF $< 50\%$, and residual LV dilatation (diastolic dimension above tolerance limit for age and weight). Operative mortality was compared between the two groups with the Fisher's exact test. Multivariate analyses were performed with the clinical and echocardiographic variables as independent variables and the presence of LV dysfunction and persistent LV dilatation as dependent variables. $p < 0.05$ was considered statistically significant.

Results

Preoperative clinical, echocardiographic, and hemodynamic characteristics of the patients are summarized in Table 1. Of 75 patients who underwent valve replacement for severe aortic regurgitation during the study period, 49 met the entry criteria. Among these 49 patients, 13 [26.5% (group 1)] displayed a preoperative diastolic dimension > 4 SD above normal (median, 61 mm; mean, 65.1 $\pm$ 8.5; range, 53–80), whereas the remaining 36 patients [73.5% (group 2)] had smaller preoperative diastolic dimensions (median, 47 mm; mean, 46.4 $\pm$ 8.7; range, 40–54). The age of the patients at the time of operation ranged between 7 and 18 years (mean, 13.9 $\pm$ 3). Five patients [10.2% (all in group 2)] were in NYHA functional class I, 36 [73.5% (6 in group 1)] in class II, 7 [14.3% (6 in group 1)] in class III, and 1 [2% (in group 1)] in class IV. All patients were in sinus rhythm. History of overt chronic heart failure was present in 1 patient in group 1. There was not any associated systemic disease in our series. In all patients, valve replacement with mechanical prostheses was performed.

Etiology

The origin of AR was rheumatic in 40.8% (20 patients). History of previous commissurotomy for aortic stenosis and progressive AR was available in 30.6% (15 patients) and in 50.3% the aortic valve was bicuspid. Aortic valve prolapse through a subaortic or subpulmonic VSD and severe AR were present in 14.3% (7 patients). Annuloaortic ectasia (e.g., Marfan's syndrome) was noted in 6.1% (3 patients), discrete subaortic obstruction damaging the aortic valve was found in 4.1% (2 patients), and rupture of sinus of valsalva was noted in 4.1% (2 patients). Surgical

Table 1. Clinical and echocardiographic characteristics of study patients[a]

Variable	Grouo 1 (preop LVD >4 SD above normal) (n = 13)	Group 2 (preop LVD <4 SD above normal) (n = 36)	p value
Male	10 (76.4)	26 (72.2)	NS
Age (Years)	14.5 ± 3.2	12.8 ± 4.5	NS
NYHA III/IV	7 (53.8)	1 (2.7)	0.05
Hx of CHF	1 (7.6)	0 (0)	NS
LVDD (mm)	65.1 ± 8.5	46.4 ± 8.7	0.005
LVSD (mm)	44.5 ± 8[b]	29.7 ± 4.4[c]	NA
EF (%)	54.8 ± 9.6	69.2 ± 8.1	0.05
Operative mortality	2 (15.3)	2 (5.5)	NS
Mean duration of follow-up (years)	2.4 ± 2.1	3.2 ± 1.8	NS

NYHA, New York Heart Association functional class; HX of CHF, history of congestive heart failure; LVDD, left ventricular end diastolic dimension; LVDD, left ventricular end systolic dimension; EF, ejection fraction; NA, not applicable; NS, not significant; preop, preoperative.

[a] Data presented are mean values ± SD or number (%) of patients.

[b] LVSD >4 SD above normal.

[c] LVSD <3 SD above normal.

Table 2. Multivariate predictors of clinical outcomes in patients undergoing aortic valve replacement for chronic severe aortic regurgitation

	p value[a]			
Variable	Operative mortality	NYHA class III/IV	Postop EF	Postop LVDD >tolerance limits
Clinical				
NYHA III/IV	0.04	NS	NS	NS
Hx of CHF	NA	NS	NS	NS
Echocardiographic				
LVEF <50%	NS	0.03	0.008	0.01
LVDD >4 SD	NS	NS	0.05	0.0003
LVSD >4 SD	NS	0.02	0.05	0.0007

NYHA, New York Heart Association functional class; Hx of CHF, history of congestive heart failure; EF, ejection fraction; LVDD >4 SD, left ventricular end diastolic dimension >4 SD above normal; LVSD >4 SD, left ventricular end diastolic dimension >4 SD above normal; Postop, postoperative; NA, not applicable; NS, not significant.

[a] $p < 0.05$ is significant in predicting outcome in combined multivariate model.

interventions on the ascending aorta were performed in 3 patients. Aortic valve replacement was performed after valvular commissurotomy at an interval of 4 years (range, 2–9).

Surgical Mortality and Complication

The mean follow-up period was 3.3 ± 2.1 years (2.4 ± 2.1 years in group 1 and 3.2 ± 1.8 years in group 2). The overall mortality rate was 8.1% [four patients (two in each group)] (Table 1). Surgical mortality was not different between groups. Death was due to low cardiac output in three patients and hemorrhage and multiorgan failure in one patient. Among them, preoperative NYHA functional class III was present in three (75%) patients, mean LVEF was 52.5 ± 2%, and mean LV end diastolic and end systolic dimensions were 55.7 ± 8.1 and 40 ± 5.2 mm (<4 vs >3 SD above normal), respectively. In the combined multivariate analysis (Table 2), only NYHA functional class III/IV was independently predictive of operative mortality ($p < 0.04$). Surgical complete heart block was noted in two patients (4.1%). During follow-up, the prosthetic valve had to be replaced in two patients (4.1%) because of bacterial endocarditis in one case and prosthetic valve malfunction secondary to thrombus formation in the other.

Postoperative Characteristics

A total of 45 patients underwent echocardiography approximately 1 year after AVR, including 11 patients in group 1 and 34 patients in group 2. Echocardiographic characteristics and changes are summarized in Table 3.

Table 3. Postoperative echocardiographic characteristics

	Group 1 (n = 11)			Group 2 (n = 34)		
Variable	Preop	Postop	Change[a]	Preop	Postop	Change[a]
EF (%)	54.2 ± 9.8	56.5 ± 9.6	NS	68.2 ± 7.8	70.7 ± 4.7	0.05
LVDD (mm)	64.4 ± 8.2	53.3 ± 8.2	0.08	45.6 ± 5	40.5 ± 4.3	0.05
LVSD (mm)	43.4 ± 7.2	37.1 ± 6	NS	28.3 ± 7.4	24.3 ± 4.2	NS

Postop, postoperative; Preop, preoperative; EF, ejection fraction; LVDD, left ventricular end diastolic dimension; LVSD, left ventricular end systolic dimension; NS, not significant.
[a] Preop vs postop (p value). Data presented as means ± SD. $p < 0.05$ is significant.

LV Function.. The postoperative improvement in EF was only significant in group 2. Persistently depressed postoperative EF (<50%) was present in 18% of patients in group 1 (2 of 11 patients). In multivariate analysis (Table 2), preoperative low LVEF ($p < 0.008$) and LV internal diameter >4 SD above normal were significant independent predictors of postoperative LV dysfunction ($p < 0.05$).

LV Internal Diameters. Postoperative LV end systolic dimension in group 1 was significantly greater than that in group 2 (>4 vs <1 SD above normal) ($p < 0.005$). Significant regression was noted in the end diastolic dimension postoperatively. However, regression was more pronounced ($p < 0.08$) in group 1 than in group 2 ($p < 0.05$). Multivariate analysis revealed that preoperative LV end systolic dimension ($p < 0.0007$), LV end diastolic dimension ($p < 0.0003$), and LVEF ($p < 0.01$) were correlated positively with residual postoperative LV dilatation (Table 2).

Clinical Status. At follow-up of both groups, two patients (18%) in group 1 and three patients (8.8%) in group 2 were in NYHA functional class III/IV ($p < 0.05$). In the combined multivariate analysis of clinical and echocardiographic variables, preoperative EF ($p < 0.03$) and LV end systolic dimension ($p < 0.02$) were significant independent predictors of postoperative functional class III/IV (Table 2). Diastolic dimension was not predictive of advanced clinical symptoms.

Discussion

Optimal timing of valve replacement for chronic aortic regurgitation has been and still is a controversial issue. Poor results after valve replacement have been demonstrated not only in preoperatively symptomatic patients but also in patients with decreased LV function [5]. Previous studies revealed that the development of significant symptoms (defined as NYHA functional class III/IV) is associated with a grim prognosis and widely accepted as a strong indication for operation [4, 5, 13]. However, the finding of LV dysfunction has led to the suggestion that objective measurements of LV status should also be used to guide the timing of operation irrespective of symptoms [1, 3, 5, 7, 11, 13]. Because most previous studies were performed on adults, we sought to determine the predictive value of preoperative functional impairment and LV size and function in postoperative persistent ventricular dysfunction and dilatation in children and adolescents. Thereby, we will be able to determine appropriate timing of valve replacement that is neither too late so that irreversible myocardial damage is established nor too early so that patients are subjected to multiple risks of reoperation.

Etiology and Preoperative Characteristics.

Similar to previous reports, the most common cause of chronic AR in this study was rheumatic heart disease (40.8%). The second most common cause of AR was progressive AR due to previous commissurotomy of the aortic valve (30.6%). Advanced preoperative clinical symptoms were observed more commonly in group 1 ($p < 0.05$), and this result is similar to those of previous reports [4, 7, 13]. This result revealed that gradual dilatation of the LV chamber, which is initially an essential compensatory mechanism to chronic volume overload of LV, could lead to severe LV dilatation accompanied by LV dysfunction. These changes will cause permanent functional impairment in patients, although the amount of time needed for this to occur is unclear and not the same for all patients. On the other hand, it should be noted that not all patients with extreme LV dilatation are severely symptomatic.

Our finding is consistent with these of Klodas et al. [7], and Michel et al. [10] showing that extreme LV dilatation is not an isolated abnormality; rather, it is usually associated with larger end systolic dimension and lower LVEF when compared with patients with smaller end diastolic dimension. However, in our study, statistically significant dif-

ferences between the two groups were only seen in ventricular EF ($p < 0.05$). Advanced symptomatic status (NYHA class III/IV) was observed more commonly in group 1, consistent with previous observations [7, 9, 10].

Postoperative Characteristics

Overall, the 8.1% operative mortality is higher than that of previous reports, in which operative mortality was approximately 4% [5, 7, 9, 13]. However, operative mortality was not significantly different between the two groups (Table 1). On multivariate analysis, the only significant predictor of operative mortality was advanced symptomatic status ($p < 0.04$), consistent with previous reports by Klodas et al. (7) and Turina et al. [13]. Consequently, with regard to operative mortality and expected improvement of LV function, extreme LV dilatation that is more common in severely symptomatic patients should not be considered a contraindication to surgery [7, 8, 10]. If patients were subjected to surgical intervention before the development of severe functional impairment, lower surgical mortality and a better improvement of clinical symptoms were obtained. Because of the small number of severely symptomatic patients in our study and the relatively short-term follow-up period, their predictive value and true long-term survival cannot be determined. Postoperative echocardiograms (approximately 1 year after operation) showed improvement of ventricular diameters and function in both groups. However, these improvements were significant only in the LV end diastolic dimension, which were more pronounced in group 1, and not significant in end systolic diameter (Table 3). The current findings are consistent with previous observations, that demonstrated a significant rate of improvement in LV size and function postoperatively [7, 10, 13]. Although patients in group 1 experienced a remarkable decrease in LV diameters, they were more likely to display persistent ventricular dilatation postoperatively than patients in group 2 ($p < 0.0003$) (Table 2). This study suggests that considerable dilatation of the LV chamber is not completely reversible and it will lead to permanent cardiac malfunction. Our results are supported by the findings of Turina et al. [13] and Klodas et al. [7] who performed studies on large series of patients with extended follow-up.

Predictors of Postoperative LV Size and Function

Persistent postoperative LV dilatation has been established as a marker of poor symptomatic outcome and increased long-term mortality [2, 7], and this may have had an impact on the survival patterns of group 1.

End Diastolic Dimension. Our study demonstrated that end diastolic dimension was a predictive factor for persistent LV dysfunction ($p < 0.05$) (Table 2). With regard to the relatively small number of patients in this study (in comparison with previous studies, especially in adults), this finding is in contrast with previous reports [5, 7, 8, 11]. Klodas et al. [7, 8] and Bonow et al. [1, 3] showed that end diastolic dimension was not predictive of the outcome and their findings lend support to the concept that LV diastolic dimension reflects the severity of the regurgitation rather than the functional consequences of the regurgitation on the myocardium. Therefore, the persistent postoperative LV dilatation most likely represents the effect of associated abnormalities, especially decreased EF and increased end systolic dimension, and they confirmed that only end systolic dimension and EF have predictive value. Thus, further studies on a larger number of pediatric patients are needed to determine the true predictive value of this important parameter.

End Systolic Dimension. Bonow et al. [2] and Klodas et al. [7] confirmed the prognostic significance of the end systolic dimension on survival and postoperative ventricular function and dilatation. They showed that end systolic dimension >55 mm was a strong predictor of persistent ventricular dysfunction and dilatation. Although most previous studies were performed on adults, they support our finding that preoperative end systolic dimension >4 SD above normal is a significant predictor of persistent ventricular dilatation ($p < 0.0007$) and dysfunction ($p < 0.05$).

LVEF. In this study, reduced LVEF ($<50\%$) was a strong predictor of postoperative dysfunction ($p < 0.008$) and persistent LV dilatation ($p < 0.01$). Similar results have been obtained from previous reports in adults [7]. Consequently, this study is consistent with previous reports demonstrating that increased end systolic dimension and reduced LVEF predict a higher rate of persistent postoperative LV dilatation, confirming the prognostic significance of these parameters on the outcome. [7, 10]

Predictors of Postoperative Clinical Status

LVEF. Our findings suggest that preoperative echocardiographic EF is a powerful determinant of postoperative symptomatic status ($p < 0.03$). This

finding is consistent with reports of Bonow et al. [1] and Klodas et al. [7] confirming the predictive value of reduced LVEF ($< 50\%$) as a poor prognostic factor. Their findings, based on long-term follow-up of a large patient cohort, suggest that preoperative LVEF is a strong determinant of outcome and the patients are afforded significantly improved postoperative survival, symptomatic status, and LV function when AVR is performed in the setting of preserved systolic function. As is shown in this study, EF also represents an essential element of the clinical and hemodynamic decision-making process in children.

Preoperative Functional Class

Turina et al. [13], Klodas et al. [7], and Michel et al. [10] confirmed that functional class has a profound effect on survival, irrespective of the contractile state. Also, we found that advanced functional impairment and worse LV performance were commonly seen in patients with preoperative NYHA class III/IV but statistically not significant (Table 2). In this regard, patients should preferentially be operated on early in the symptomatic course of AR and before severe symptoms develop. Unfortunately, the population of our patients with NYHA class III/IV was relatively small (8 of 49 patients), so postoperative outcome and clinical status cannot be predicted accurately. Further studies on a larger number of severely symptomatic pediatric patients are needed to determine true predictive value of advanced clinical status.

Study Limitations

The use of echocardiography for determining ventricular dimensions and function may be considered a limitation. However, the methodology during the period analyzed was stable, measurements of LV dimensions were always guided by two-dimensional echocardiography, and only high-quality measurements were accepted. Similar data have been used in previous studies and have served as the basis for recommending the timing of AVR [5, 7, 11].

The patients considered in this study represented only few percent of all people suffering from chronic severe AR who have undergone valve replacement. In other words, we did not represent clinical and hemodynamic characteristics of patients with mild to moderate AR. Because of the small number of patients and relatively short-term follow-up period, the results must be considered with caution. Also, the natural history and late survival could not be analyzed.

Conclusions

Our findings are consistent with those of previous reports in which preoperative characteristics have significantly predicted early postoperative outcome, thus indicating the prognostic utility of objective LV size and performance assessment in the setting of AR. In chronic AR, preoperative NYHA class III/IV is the main predictor of surgical mortality. The presence of NYHA class II/III symptoms should be a strong incentive to consider closed follow-up of patients. In addition, the hemodynamic state of myocardium, represented by internal ventricular dimensions and LVEF, was the best predictor of persistent ventricular dysfunction and dilatation postoperatively. With respect to ventricular size, both end systolic and end diastolic dimension > 4 SD above normal have prognostic capacities for persistent LV dysfunction, and these parameters can be considered as markers of irreversible dysfunction. Importantly, echocardiographically determined LVEF $< 50\%$ is a powerful predictor of permanent systolic dysfunction.

It is worth noting that clinical symptoms, systolic LV function, and ventricular size are three independent variables, and these parameters do not necessarily progress concomitantly in patients with severe chronic AR.

Ideally, surgical correction of aortic regurgitation in children, similar to adults, should be performed before severe LV dysfunction occurs. Operation can be performed in severely symptomatic patients and/or in those with greatly impaired hemodynamic function, but surgical mortality is higher and postoperative improvement is not optimal.

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